EARLY GASTRIC CANCER IN YOUNG, ASYMPTOMATIC CARRIERS OF GERM-LINE E-CADHERIN MUTATIONS

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ABSTRACT

Background  Germ-line truncating mutations in the E-cadherin (CDH1) gene have been found in families with hereditary diffuse gastric cancer. These families are characterized by a highly penetrant susceptibility to diffuse gastric cancer with an autosomal dominant pattern of inheritance, predominantly in young persons. We describe genetic screening, surgical management, and pathological findings in young persons with truncating mutations in CDH1 from two unrelated families with hereditary diffuse gastric cancer.

Methods  Mutation-specific predictive genetic testing was performed by polymerase-chain-reaction amplification, followed by restriction-enzyme digestion and DNA sequencing in Family 1 and by heteroduplex analysis in Family 2. A total gastrectomy was performed prophylactically in five carriers of mutations who were between 22 and 40 years old. In each case, the entire mucosa of the stomach was extensively sampled for microscopical analysis.

Results  Superficial infiltrates of malignant signet-ring cells were identified in the surgical samples from all five persons who underwent gastrectomy. These early diffuse gastric cancers were multifocal in three of the five cases, and in one person infiltrates of malignant signet-ring cells were present in 65 of the 140 tissue blocks analyzed, representing in aggregate less than 2 percent of the gastric mucosa.

Conclusions  We recommend genetic counseling and consideration of prophylactic gastrectomy in young, asymptomatic carriers of germ-line truncating CDH1 mutations who belong to families with highly penetrant hereditary diffuse gastric cancer.

FAMILIAL diffuse gastric cancer is a disease with autosomal dominant inheritance in which gastric cancer develops at a young age. Germ-line truncating mutations in the E-cadherin gene (CDH1) have been found in several families with hereditary diffuse gastric cancer. Analysis of these families indicates that gastric cancer develops in three of every four carriers of a mutant CDH1 gene. Predictive genetic testing is therefore possible in these families, which raises the question of whether carriers of the mutation should undergo clinical surveillance and even prophylactic surgery. We describe genetic screening, surgical management, and pathological findings in young persons with a CDH1 mutation from two unrelated families with hereditary diffuse gastric cancer.

CASE REPORTS

Family 1

The proband in Family 1 (Subject IV-4), previously described by Gayther et al., was a 24-year-old woman with a family history of gastric cancer (Fig. 1) who presented with left subcostal pain. Gastroscopy revealed mucosal hyperemia and friability. Multiple biopsy samples were histologically normal. Six weeks later, she returned with anorexia, weight loss, and abdominal bloating. A second gastroscope examination again showed hyperemia but no focal lesions. Colonoscopy revealed bumpy mucosa at the splenic flexure that was shown on computed tomographic scanning to be consistent with tumor infiltration. A diagnosis of metastatic signet-ring–cell carcinoma was made on the basis of laparotomy and biopsy. A course of chemotherapy was initiated, but the subject died five months after the initial presentation. At autopsy, the gastric wall was markedly thickened because of infiltration by diffuse carcinoma.

The proband's mother (Subject III-1) had died of metastatic gastric cancer when she was 29 years old. She had presented at 25 years of age with vague dyspeptic symptoms. No abnormalities were detected by a barium contrast study of the upper gastrointestinal tract. Three years later, she returned to the physician with postprandial epigastric pain. A second barium study showed a mucosal defect in the lesser curvature, and biopsy revealed diffuse gastric cancer. She underwent chemotherapy but died within seven months.

The proband’s maternal grandmother (Subject II-1) died of gastric cancer at the age of 32, her great-grandfather (Subject I-2) died of gastric cancer at the age of 45, and her great aunt (Subject II-3) died of gastric cancer at the age of 39 (Fig. 1). A diagnosis was made of a familial predisposition to gastric cancer with an autosomal dominant pattern of inheritance. The proband had two older sisters (Subjects IV-1 and IV-2) and a twin sister (Subject IV-3), all of whom were referred to a medical geneticist, who recommended a program of endoscopic screening. Subject IV-3 was asymptomatic, and both gastroscopy and random biopsies revealed no abnormality. She was concerned about the sensitivity of the procedure and requested a gastrectomy. The monoygosity of Subjects IV-3 and IV-4 was confirmed by means of a panel of six highly polymorphic DNA markers (data not shown).

Three months after the negative gastroscopy, an elective total gastrectomy was performed.

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gastrectomy with Roux-en-Y esophagojejunostomy was performed in Subject IV-3. The stomach was grossly normal. Multiple sections were taken from all regions of the stomach. Microscopic foci of intramucosal diffuse carcinoma were identified in two adjacent blocks from the gastric cardia (Fig. 2C and 2D). Seven years later, Subject IV-3 is free of disease, and repeated endoscopic examinations and biopsies of the esophagojejunostomy site have revealed no cancer.

Family 2

The proband of Family 2 (Subject IV-3), previously described by Gayther et al., presented at 38 years of age with mild epigastric distress. She had a strong family history of gastric cancer (Fig. 3) and was therefore concerned that she might also be affected. A prophylactic total gastrectomy was performed. The stomach was histologically normal. Her half-brother (Subject IV-1) died of diffuse gastric cancer at the age of 44. Her half-sister (Subject IV-2) presented with vague abdominal symptoms at the age of 36. Seven years later, after multiple negative endoscopies, she requested an open gastric biopsy, which revealed diffuse gastric cancer. She underwent a total gastrectomy. The lymph nodes and the margins of the resection were free of cancer, and she was free of disease at this writing, eight years later.

The proband’s sister (Subject IV-4) was diagnosed with diffuse gastric cancer at the age of 36 by open biopsy after a negative endoscopy. She underwent a total gastrectomy and was free of disease at this writing, eight years later. The mother of these subjects (Subject III-2) and three of her four siblings had gastric cancer. Subject III-2 died of metastatic diffuse gastric cancer at the age of 69, one year after undergoing gastrectomy for diffuse gastric cancer. One of her brothers (Subject III-5) died of diffuse gastric cancer when he was 32 years old. Her twin sisters, Subjects III-6 and III-7 (zygosity unknown), died of diffuse gastric cancer. Subject III-6 died when she was 32 years old, two months after receiving a diagnosis of diffuse gastric cancer. Subject III-7 had a prophylactic subtotal gastrectomy at the age of 32. She died of metastatic diffuse gastric cancer originating from the unresected gastric cardia when she was 56 years old.

METHODS

After informed consent (written in the case of Family 1 and oral in the case of Family 2) was obtained, DNA was extracted from the peripheral blood of Subjects IV-3 and IV-4 in Family 1 and from Subjects III-1, III-2, III-3, IV-2, and IV-4 in Family 2 by phenol-chloroform extraction. Mutation analysis was performed as previously described.6,11 In both Subject IV-3 and her twin sister, Subject IV-4 (Family 1), there was a single-strand conformation polymorphism band shift in exon 12. DNA sequencing revealed a C2095T nonsense mutation (R598X), which destroys a TaqI restriction site.
striction site. In Family 2, analysis of the exon 11 amplicon revealed a heteroduplex band in three affected persons but not in the two unaffected spouses of Subject III-2. This band results from a 1171insG mutation, which creates a frame shift predicted to truncate the protein at codon 587.

A program of genetic counseling and DNA testing was provided to the other members of both families. In Family 1, predictive genetic testing was performed on the proband’s older sisters (Subjects IV-1 and IV-2) by digestion of the polymerase-chain-reaction amplicon with TaqI and DNA sequencing (Fig. 1). In Family 2, predictive testing by heteroduplex analysis was offered to 14 persons, including 13 first-degree relatives of the affected, presumed, or proven carriers of the mutation, 1 of whom (Subject IV-3) had previously undergone prophylactic gastrectomy (data not shown).

RESULTS

In Family 1, Subject IV-1 was a carrier of the mutation, and her sister Subject IV-2 tested negative. Subject IV-1, who was 35 years old at the time, had undergone yearly endoscopic examinations with multiple random gastric biopsies since she was 29 years old. After receiving counseling from a geneticist, a surgeon, and a dietician, she decided to undergo elective gastrectomy. A total gastrectomy with Roux-en-Y esophagojejunostomy was performed 15 months after her last gastroscope examination. The procedure was well tolerated, and she was discharged from the hospital after one week.

The gastrectomy specimen was grossly normal both in appearance and by palpation. The whole stomach was sectioned, embedded in paraffin, and examined microscopically. Superficial infiltrates of malignant signet-ring cells were present in 65 of the 140 tissue blocks (Fig. 2A and 2B). No focus was larger than 8 mm in diameter, and the affected blocks were noncontiguous. In aggregate, the foci of cancer represented less than 2 percent of the gastric mucosa. Many of the foci were less than 1 mm in diameter, and all lay under normal-appearing surface epithelium. The carcinoma was present within 7 mm of the esophageal margin and within 13 mm of the duodenal margin of the resection. There was no lymphatic or vascular invasion, and all lymph nodes were free of metastasis in all three cases. Subject IV-3, the proband, who had a prophylactic gastrectomy before genetic testing was available, does not carry the mutation. She was relieved to hear that she was not a carrier of the mutation, because it means her descendants are not at risk.

In Family 2, 5 of the 14 persons tested carried the 1171insG mutation. After extensive counseling sessions, three of the five carriers of the mutation decided to undergo prophylactic total gastrectomy with reconstruction of the gastrointestinal tract by means of a Roux-en-Y esophagojejunostomy. The subjects’ ages at gastrectomy were 22 years, 28 years, and 40 years (Fig. 3). All incisions healed well, and all three subjects returned to work within four months.

The three gastrectomy specimens were grossly normal but contained foci of early diffuse gastric cancer detected by complete microscopical examination of the gastric mucosa. These lesions were all characterized by infiltrates of signet-ring cells in the superficial portion of the lamina propria (Fig. 2F, 2G, and 2H). Early gastric cancer was unifocal in Subject V-3 and multifocal in Subjects V-1 and IV-6, with infiltrates present in several noncontiguous tissue blocks. There was no lymphatic or vascular invasion, and all lymph nodes were free of metastasis in all three cases. Subject IV-3, the proband, who had a prophylactic gastrectomy before genetic testing was available, does not carry the mutation. She was relieved to hear that she was not a carrier of the mutation, because it means her descendants are not at risk.

DISCUSSION

We describe five persons from two families with an inherited susceptibility to diffuse gastric cancer who underwent prophylactic total gastrectomy. Although these operations were prophylactic in intent, their outcome was presumably curative. In all five cases, neoplastic lesions that were undetected on gross examination were found only after extensive pathological studies of the gastrectomy specimen. These five cancers, which contained malignant signet-ring cells, were examined by two pathologists. In four of the gastrectomy specimens the entire gastric mucosa was examined, and in one case this required the processing of more than 200 tissue blocks. The signet-ring–cell infiltrates appeared either as isolated cells or in small clusters in the lamina propria underlying normal-appearing surface epithelium (Fig. 2). In three cases, multiple infiltrates were identified, including microscopic lesions less than 1 mm in diameter. In situ signet-ring
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A
Family 1, Subject IV-1

B
Family 1, Subject IV-1

C
Family 1, Subject IV-3

D
Family 1, Subject IV-3

E
Family 1, Subjects IV-1 and IV-3

F
Family 2, Subject IV-6

G
Family 2, Subject V-1

H
Family 2, Subject V-3
infiltrates were also present in both gastrectomy specimens from Family 1 (Fig. 2E). The natural history that these early cancers would have followed if they had been left untouched will never be known, but it is likely that at least some of them would have become clinically evident.

In both families we found truncating CDH1 mutations that would be expected to disrupt the function of the E-cadherin protein. Inactivation of the second (wild-type) allele in a somatic cell of the gastric mucosa, as is observed with classic tumor-suppressor genes, would lead to a total loss of E-cadherin. In cases of hereditary diffuse gastric cancer, the wild-type allele could be inactivated by either a point mutation or CDH1 promoter hypermethylation. The carriers of the mutations in these families had a highly penetrant cancer-susceptibility phenotype, and gastric cancer developed in all obligate carriers of mutations except Subject II-1 and possibly Subject II-6 in Family 2. Genetic testing was performed within the context of a program of counseling, as described in the guidelines of the International Gastric Cancer Linkage Consortium.

The clinical options available for carriers of germline CDH1 mutations are limited because of the current difficulty of detecting diffuse gastric cancers at an early, treatable stage. Diffuse gastric carcinomas often underlie a grossly and histologically normal surface epithelium (as in the cases described here), which makes it difficult to detect small lesions by endoscopy. Four of the five gastrectomies were performed within 15 months of an unrevealing endoscopic examination. The lesions were not identifiable by gross examination of the stomach mucosa in any of the prophylactic-gastrectomy specimens with diffuse gastric cancer. Random biopsies had also failed to reveal the cancers in Family 1.

Since no marker is available for early detection, pro-
Phylactic gastrectomy seems reasonable for the carriers of mutations in families with highly penetrant mutations. It seems prudent to consider gastrectomy at an age younger than that of the youngest affected person in the family. We would not recommend prophylactic gastrectomy for members of a family with hereditary diffuse gastric cancer in which a causative mutation has not been identified or for members of families with less highly penetrant forms of susceptibility to gastric cancer.

Prophylactic surgery is an important part of the management of other syndromes of susceptibility to cancer. Prophylactic mastectomy greatly reduces the risk of breast cancer, and both prophylactic mastectomy and, to a lesser extent, prophylactic oophorectomy are predicted to increase the life expectancy of carriers of BRCA1 or BRCA2 mutations. Prophylactic thyroidectomy to prevent medullary thyroid carcinoma is the standard of care for children from families with multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma who have mutations in the RET proto-oncogene. In cases of familial adenomatous polyposis coli syndrome, prophylactic colectomy is currently the only means of preventing colorectal carcinoma. Colectomy extends the life expectancy of patients with this syndrome and exposes them to other related risks, such as duodenal, gastric, or biliary carcinomas. Gastrectomy may extend the life of persons who are at risk for hereditary diffuse gastric cancer and thereby expose them to the risk of other cancers; for instance, lobular breast carcinoma has not been identified or for members of families with familial gastric cancer. Screening has been recommended to the female carriers of mutations in the families we studied.

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